Remarks

The claims have been amended to delete reference to cellulose as a substrate. This amendment adds no new matter to the claims.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 43-46, 49-53, and 56 were rejected under 35 U.S.C. §112, second paragraph, as indefinite on the basis that the claim lists cellulose as a substrate, and simultaneously states that the substrate is free of polysaccharides. Claim 43 has been amended, as suggested by the Examiner, to delete cellulose as a possible substrate.

Rejections under 35 U.S.C. §103 (a)

Claims 43-46, 49-53 and 55 were rejected under 35 U.S.C. §103 as purportedly being obvious over U.S. Patent No. 5,788,987 to Busetti et al. ("Busetti") in view of U.S. Patent No. 5,958,458 to Norling et al. ("Norling"). Claims 56 and 57 were rejected under 35 U.S.C. §103 as purportedly being obvious over Busetti in view of Norling and U.S. Patent Application Publication No. 2003/0050228 to Ekwuribe et al. ("Ekwuribe"). These rejections are respectfully traversed if applied to the amended claims.

Analysis of the Rejection of Claims 43-46 and 49-53, and 55

The purported basis for the rejection is that Busetti discloses cores with drugs, such as insulin, formed of components including dihydrogen calcium phosphate dihydrate, and Norling discloses coated cores. Thus, the Office Action purports that it would have been obvious to modify Busetti and place the insulin on the core, rather than in the core.

Busetti discloses numerous drugs that can be present in a core, as well as numerous excipients that can be blended with these drugs, to treat a variety of early-morning pathologies.

Dibasic calcium phosphate dehydrate is one of several listed excipients. Insulin is one of numerous listed drugs. Busetti discloses the dibasic calcium phosphate dihydrate for a known use, as an excipient in tablets where the drug and excipient are mixed together, not for a previously undescribed use, that being its use as a drug-coated core.

Busetti discloses that the compositions can be used to treat an early morning pathology. The methods involve administering a time-specific controlled release dosage formulation prior to sleep, which delivers a pharmaceutically active agent at about the time of awakening or a few hours in advance of awakening. To achieve these ends, Busetti uses a time-specific controlled release dosage formulation that includes (1) a core including the pharmaceutically active agent(s) effective for the treatment of the early morning pathology, and (2) a swellable polymeric coating layer substantially surrounding the core. The swellable polymeric coating layer delays the release of the pharmaceutically active agent from the core for a predetermined period of time dependent upon the thickness of the swellable polymeric coating layer, to effect delivery of the pharmaceutically active agent at the more appropriate time (e.g., at about the time of awakening).

Non-Obviousness on the Basis of Lack of Expectation of Success

There would be no motivation to modify Busetti as the Office Action suggests, or any expectation of success in doing so, by placing the drug on a coating rather than in a core.

Although Busetti discloses numerous materials that can be present in the core (i.e., numerous drugs and numerous excipients), the claims are limited to a core of dibasic calcium phosphate dehydrate coated with insulin. Accordingly, the only potentially relevant portion of Busetti is that which relates to the use of dibasic calcium phosphate dehydrate in the core, which dibasic calcium phosphate dihydrate is blended with insulin to form the core.

Thus, among a myriad of other possibilities, Busetti discloses placing a blend of insulin and excipient (in this case, dibasic calcium phosphate dihydrate) in the core, and coating the core with an enteric coating. Once the enteric coating is released, the rate of insulin release depends on the release of insulin from the blend of insulin and dibasic calcium phosphate dehydrate. Dibasic calcium phosphate dehydrate is largely insoluble, so the rate of release from a core formed of a blend of insulin and dibasic calcium phosphate dihydrate is relatively slow. In contrast, where a dibasic calcium phosphate dehydrate core is coated with insulin (as is claimed), the release of insulin does not depend on the solubility or insolubility of dibasic calcium phosphate dehydrate. It relates to the solubility of the active that is present on top of the core (i.e., the core is not relevant, because the drug coating is released before the core is solubilized).

If the drug is present in the coating rather than inside the core, the drug release kinetics change. The effect on drug delivery will be relevant, in that the drug release kinetics will be quite different from controlled/sustained/delayed release (i.e., drug delivery will be faster).

Once any enteric coating on the core is released, a drug present in a coating on a core is instantly accessible, and thus released quickly. A drug mixed with an excipient within the core is release as the core dissolves, which depends on both the dissolution of the drug and the excipient. The latter release pattern is slower than the former. Thus, there would be no expectation of success at arriving at suitable release kinetics for early morning administration if Busetti were altered as suggested by the Examiner.

This is somewhat analogous to a Tootsie pop® (a lollipop with a chocolate center). You don't get to the chocolate center until the candy coating is removed, but you have instant access

to the candy coating. However, if the candy and the chocolate are blended together, one cannot access all of the candy until all of the chocolate is released.

Furthermore, Busetti teaches a nighttime administration of insulin, which, when the core is a blend of insulin with dibasic calcium phosphate dehydrate (and the enteric coating is released), is a sustained release insulin formulation. In contrast, the claimed insulin-coated dibasic calcium phosphate dehydrate core would be a fast-release insulin formulation (at least after an enteric coating, if present, is released). These release rates are not the same, and the differences would potentially have profound effects on the patient (indeed, diabetics are often dosed with two different kinds of insulin, quick release and sustained release, and these are not considered the same or equivalent types of insulin). Bolus administration of insulin, while the patient is asleep, could have profound implications.

Even with the controlled release taught by Busetti, it may be unwise to administer insulin in a night-time formulation. That is, patients taking insulin must carefully monitor their blood sugar throughout the day, and adjust dosages of insulin accordingly. If they do not do so, they risk going into insulin shock. Insulin shock, also known as hypoglycemia, occurs when a diabetic either takes too much insulin, doesn't eat frequently enough, or doesn't eat sufficient amounts of sugar.

It might be potentially dangerous to take an oral insulin tablet before going to bed, with the expectation that the insulin levels in the patient's system upon waking are suitable (the best case scenario under Busetti). Coupling this issue with the potential for altering the release kinetics by placing the insulin on a coated core, rather than as a blend with an excipient in the core, might prove to be a serious detriment.

This is particularly true where, as here, the release of the active when it is outside of the core would be expected to be faster than if it is inside the core (i.e., where degradation of the core provides controlled release). That is, this modification might provide a bolus administration of insulin at a time when there is no monitoring of insulin levels (i.e., patients do not ordinarily monitor their insulin levels when they are asleep), and at a time when blood sugar levels are low (i.e., diabetes patients may tend to sleep at night, rather than eat at night).

Importantly, once the enteric coating is released, there would be no expectation that placing the drug on the core, rather than in the core, would provide the requisite early morning drug delivery, because the fast release from the insulin from the coated core might release all of the insulin before morning. Busetti not only teaches away from providing a bolus insulin administration during the night or in the early morning, such a modification would likely be detrimental to a sleeping patient. Thus, there can be no motivation to modify Busetti as the Examiner has suggested.

Norling does not overcome the above-listed failures of Busetti to teach the claimed invention. Norling has merely one sentence that suggests placing a drug in a coating (Column 11, lines 57-67). The crux of Norling's disclosure relates to placing a drug in the core, and, indeed, Norling states "As mentioned above, the cores contained in a formulation according to the present invention comprise a pharmaceutically acceptable inert carrier and an active substance." Taking Norling as a whole, one would still blend the drug with the core, as that is the crux of what Norling teaches.

Given the potential health concerns associated with night-time administration of oral insulin, the one word disclosure of "insulin" in Busetti, as one of many types of agents that can be

administered, does not render obvious the claimed invention, alone or in combination with Norling. Norling cannot properly be combined with Busetti in a way that thwarts the very purpose of Busetti, namely, the night-time administration of active agents for early morning delivery of the agents. Given the concerns raised above, neither Norling nor Busetti provide any teaching, suggestion, or motivation to change the release kinetics of a night-time insulin formulation a would occur if the insulin were placed on the core, rather than in the core. Given the expected change in release kinetics, it would appear that Busetti would teach away from doing so, as the expected faster release might be detrimental to the patient, and teaching away is the antithesis of obviousness.

Other than listing insulin in a laundry list of agents to be administered, Busetti provides no further information on how insulin control can be achieved, or whether the therapy is appropriate for diabetics.

Given a) Busetti's failure to teach coating insulin onto a core, b) Busetti's failure to teach that one could even adhere insulin to the core and adhere the extended-release coating to the insulin layer, c) the uncertain (and potentially dangerous) effect on the release rate of the insulin when one goes from a blended core to a coated core, and d), the danger of administering insulin in a night-time fashion without blood-sugar testing (which ordinarily would not occur while the patient is asleep), it would require the benefit of hindsight to arrive at Applicants claimed formulation. Further, even if one did arrive at Applicants claimed formulation with the benefit of hindsight, it would appear to thwart the express purpose of the primary reference (Busetti), that being a specific type of delivery.

For at least these reasons, Applicants respectfully request that the Examiner withdraw this ground of rejection.

Analysis of the Rejection of Claims 56 and 57

With respect to Claims 56 and 57, the same arguments presented above with respect to Claims 43-46 and 49-53, and 55.

Further, it would not have been obvious in view of either Busetti or Norling to use the HIM-2 version of insulin of Ekwuribe. If Busetti's or Norling's formulations were sufficient to administer insulin orally, without chemically modifying the insulin, then it would not have been necessary to prepare a specifically modified form of insulin, specially adapted for oral administration. This additional modification requires significant additional effort and expense. Applicants submit that it would not be obvious to have done so, due to a lack of motivation to do so. That is, there is no motivation to use exotic materials, such as those described in the secondary reference (Ekwuribe), when the primary reference (Norling) teaches that ordinary, unmodified materials will suffice.

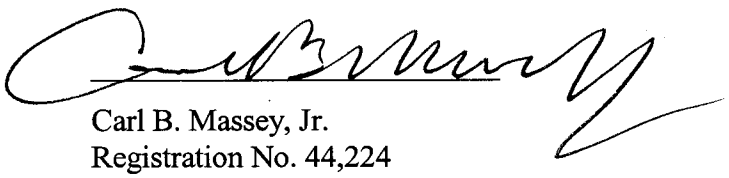
For at least these reasons, Applicants submit that Claims 56 and 57 are non-obvious.

Conclusion

Applicants respectfully submit that the claims as amended are in condition for allowance, and acknowledgment of same is earnestly solicited. If the Examiner disagrees, he is encouraged to contact the undersigned Applicants' representative.

Respectfully submitted,

Date: October 29, 2007



Carl B. Massey, Jr.
Registration No. 44,224
For
David S. Bradin
Registration No. 37,783

WOMBLE CARLYLE SANDRIDGE & RICE
P. O. Box 7037
Atlanta, Georgia 30357-0037
(404) 872-7000
(919) 484-2382 (direct dial)
(919) 484-2084 (facsimile)